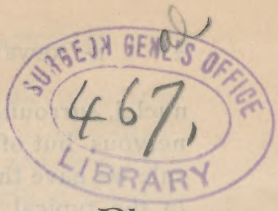

Report of the Section on Anatomy, Physiology and Pathology.

RECENT DISCOVERIES IN THE PHYSIOLOGY OF GANGLION CELLS.

By H. Newell Martin, M. A., M. D., D. Sc., F. R. S.,
Chairman.

It has been the custom for the chairman of the section which I have the honor to represent to-day to search recent physiological literature for some topic which may be of special interest to medical men. The literature of physiology is now so voluminous, and one has to seek it in so many journals, that even the physiologist himself cannot keep abreast of it, much less the busy practitioner. On making such a search it occurred to me that some work done during the last three years on the structure of ganglion cells and the changes undergone by ganglion cells when they were irritated would have interest for you, especially as it seems to open up quite new branches of research in the pathology of the nervous system.

Thanks to the work of Heidenhain and Langley, we have known for several years that the cells of a gland at work differ in their microscopic appearance, and differ in their staining qualities, from the cells of a gland at rest; and it occurred to Mr. Hodge—then at the Johns Hopkins, now at the Clark University—it occurred to him to see if he could not discover whether histological changes take place in ganglion cells when they are stimulated.

I may use a moment in recalling to your memory the structure of the typical spinal ganglion cell, the cell marked A in the diagram. There you see the capsule, with its many

nuclei, surrounding the cell, generally supposed not to be nervous but of connective tissue nature. Within the capsule we have the general granular cell substance, containing in the typical cell a rounded well defined nucleus, sharply marked off from the general protoplasm of the cell and with a single nucleolus in it. When prepared as this specimen was, by the aid of osmic acid, the nucleus shows a few darkly stained points around the nucleolus, but most of it remains clear and unstained and is a conspicuous whitish object in the general darkly stained mass of the osmic acid specimen.

It will hardly be necessary for me to go into details as to Dr. Hodge's earlier work, because, like most work of the kind, one has to begin tentatively and find out the best methods and the way to get the best results. In general I may say that his hardening was done by alcohol, and his subsequent staining either by osmic acid or by what is known as the Gaule method, which those of you who are histologists will remember. His work does not constitute the first set of observations made on histological changes produced in ganglion cells by various conditions. Some researches had been made on nerve cells at rest compared with ganglion cells in pathological conditions, with the result that the most marked changes in the cell were found in the nucleus; and some ten or eleven months after Dr. Hodge published his preliminary communication in the American Journal of Psychology, there appeared a paper in which observations were made by stimulating one sciatic nerve in a frog while leaving the other at rest, and subsequently comparing sections of the two sides of the spinal cord to see if the cells differed in appearance; it was found that the nuclei of the cells on the two sides were a little different in their relation to staining fluids. It had also been noticed that in starved animals the nuclei of the nerve cells seemed shrunken and the protoplasm less dense, more or vacuolated than normal; but Dr. Hodge was the pioneer in the discovery that stimulation of normal ganglion cells caused changes in them, which could be recognized with the aid of the microscope.

His work has been continued at Clark University with the greatest care. In order to get comparative results it

was necessary to know the strength of the electrical stimulation, (that he used electrical stimulation I need hardly say). That was done by aid of galvanometer and rheochord, and every device was used to keep the strength of the stimulating current uniform. Then apparatus was devised to secure that the number of stimulations given in a second to the nerve was always the same : so each animal so far as one can assume that one young cat is like another young cat was brought under practically the same conditions.

His first idea was to etherize or curarize the animal in order to keep it quiet ; but observations on animals who had been given curare or ether showed that those drugs brought about changes in the nerve cells apart from all extrinsic nerve stimulation ; so it was necessary to eliminate their use. That was done by a method devised by Ludwig some years ago, in which a small hole is trephined in the skull of the animal, then a thin blunt glass rod introduced and passed through the brain until it reaches the crura cerebri. Both crura are destroyed by moving the rod to and fro, and thus all motor and sensory paths from the cerebral hemispheres to the lower parts of the body are cut off. After the operation the animal immediately goes into a state of apparently sound quiet sleep, and under those conditions it is experimented upon. Dr. Hodge used kittens, and each animal was carefully packed in cotton batting after destruction of the crura and its temperature observed from time to time and kept as constant as possible. So far as I can see every precaution to ensure reliable results was taken.

Next, the brachial plexus was exposed on the right side of the body and placed between electrodes and, by clockwork during the continuance of the excitation, the nerve was stimulated for fifteen seconds out of every minute, and rested the remaining forty-five ; and so on, minute after minute ; thus in five hours stimulation the nerve would have had on the whole an hour and fifteen minutes of stimulation, and during the remainder of the time would have been at rest. The lower part of the nerves going from the brachial plexus to the muscles of the forelimb was not divided, and

the test that the sensory fibres were probably active was that the muscles always moved when the stimulus was applied. Since the muscles responded to the stimulus, showing the motor fibres were irritable, it was assumed that the sensory fibres going to the spinal ganglion were also irritable.

Working in this way Dr. Hodge found on staining the ganglion cells remarkable changes; those changes are of three kinds, and come on in different order. In the first place, the nucleus of the stimulated cell loses its well defined contour, and takes more of the appearance of the nucleus of the figure marked B in the diagram. In the second place, the body of the cell loses its general dark granular appearance and becomes vacuolated, filled apparently with little spaces containing liquid, instead of the ordinary granules which normally fill the interstices of the meshwork of fibrils which constitute the essential part of a ganglion cell. Third, and most remarkable, though Dr. Hodge only refers to it and does not attempt to explain it, the nuclei of the capsule which surrounds the ganglion cell and are not part of it at all, undergo changes. They shrink and become spherical rather than oval. It may be that the waste products secreted by the stimulated nerve cell affect these nuclei of its capsule.

Dr. Hodge takes up next the question whether these changes are physiological and not pathological; whether they are due to this gross method of electrical stimulation; which must be more crude than the normal afferent nerve impulse: if normal, the changes ought to be progressive with increase of the time of stimulation. This he tested by having the nuclei measured by persons who did not know what had been done to the cells, who did not know anything about the object of the research, but simply sat down to measure nuclei in their diameter: the concurrent testimony of these observers shows that the diminution of the diameter of the nuclei increases as the time of stimulation increases. If you stimulate one hour you will get perhaps an average diminution in volume of the nuclei as calculated from their diameters of about fifteen per cent. If you stimulate two hours, the diminution is not much more marked. If you stimulate four hours, the average diminution in volume of

the nuclei of the stimulated side is thirty-five per cent., and after prolonged stimulation of eight hours, sometimes the diminution in volume was as much as sixty per cent.

One point that is important I omitted to mention in its proper place. As soon as the stimulation is finished the kitten is killed as quickly as possible, the eighth cervical ganglion on each side excised and the two put together in the same hardening fluid, they are fixed together on the same slide, stained in the same vessel, mounted side by side in the same paraffine, and cut with the same stroke of the knife, so that as far as any action of any reagent on the ganglion of the right side which had been stimulated, and on the ganglion of the left side which was left at rest, there is no possibility of the reagents producing any of the differences observed.

Next came the thought, if this change in the ganglion cells be really a result of their physiological activity, if they lose matter and alter their structure during functional activity, then they ought to recover with rest, and the recovery ought to be proportionate to the time of rest; and in a paper which has just appeared in the last number of the Journal of Psychology Dr. Hodge discusses that question.

Taking a number of kittens, from six to eight weeks old, they were well fed and then experimented upon; after experiment they were given no food until they were killed. Each animal was used for five hours, each minute of each hour indicating fifteen seconds of stimulation and forty-five seconds of rest. Then one kitten was killed at once, another was kept an hour before it was killed, a third two hours, and so on. The general result was this: In the kitten killed immediately, there was very great histological difference between the ganglion of the stimulated and unstimulated side. In the kitten killed an hour later the difference was less, the nucleus had begun to enlarge again, and did not stain quite so deeply with osmic acid; and so it went on hour after hour, but even at the end of eighteen hours the nucleus on the stimulated side was smaller than the nucleus on the rested side. At the end of twenty-four

hours, however, most of the nuclei of the right ganglion (the stimulated one), had returned to the histological condition of the normal resting ganglion cell.

I have received within the last few days a note from Dr. Hodge, in which he says he is now applying this method to the normal alternations of rest and work in animal life. He first tried it with kittens and cats, but it is very difficult to get animals of that kind to sleep any definite nnmber of hours. It occurred to him that birds had more regular habits as to sleeping and waking hours than any other animals. He tells me, though not ready for detailed publication, that he finds very distinctly in English sparrows the same difference in ganglion cells at the end of a day, as compared with the ganglion cells of a sparrow killed early in the morning, that he finds between the rested and stimulated ganglion cells in the kitten.

It seems to me that this method of research which proves that one can discover by histological methods what special nerve centre has been active, combined with the recent discovery of Langley that we can by local application of nicotine throw certain ganglia out of functional activity for a time, puts us on a whole new course of investigation, or two new courses of investigation in regard to the physiology and pathology of the nervous system. Ultimately I think these methods will come to be used largely in the localization of nerve function instead of the more gross surgical methods we have now at our disposal. With this future prospect it seemed to me that it might interest you to hear about them : and that is my excuse for intruding upon your time to-day.